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Model of Competitive Binding of Vascular Endothelial Growth Factor and Placental Growth Factor to VEGF Receptors on Endothelial Cells

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Experiments show that placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) can act synergistically on endothelial cells, with PlGF augmenting the response to VEGF both in *in vivo* models of pathological angiogenesis and in *in vitro* models of endothelial cell survival, migration and proliferation. Because PlGF competes with VEGF for binding to VEGF receptor-1 (VEGFR1), but does not bind VEGFR2, this synergy has been hypothesized to be due to a combination of two mechanisms. First, PlGF may initiate signaling through VEGFR1. Second, PlGF may displace VEGF from VEGFR1 to VEGFR2, causing increased signaling through VEGFR2. In this computational study, the relative contribution of PlGF-induced VEGF displacement to the synergy is quantified, using a mathematical model of ligand-receptor binding to examine the effect on ligand-receptor complex formation of VEGF and PlGF acting together. In particular, the model is used to simulate, *in silico*, a specific *in vitro* experiment in which VEGF-PlGF synergy is observed. We show that whereas a significant change in the quantity of endothelial cell surface growth factor-VEGFR1 complexes is predicted in the presence of PlGF, the increase in the number of VEGFR2-containing signaling complexes is less significant. These results were also shown to be robust to significant variation in the kinetic parameters of the model. Synergistic effects observed in that experiment thus appear unlikely to be due to VEGF displacement, but to a shift from VEGF-VEGFR1 to PlGF-VEGFR1 complexes and an increase in total VEGFR1 complexes. These results suggest that VEGFR1 signaling can be functional in adult-derived endothelial cells. Parameters specific to the VEGF-PlGF system were used based on published data. This is the first such computational model of the VEGF family and their receptors.